Selected classical and novel antiepileptic drugs – mechanisms of action, neuroprotection, and effectiveness in epileptic and non-epileptic conditions

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SUMMARY

Introduction. One of the most common neurological disorders is epilepsy, characterised by recurrent spontaneus seizures. Although not fully efficient in ca 30% of patients, pharmacologic treatment of epilepsy plays an important therapeutic approach not only against epilepsy.

Aim. To provide data on the mechanism of action, activity and neuroprotective efficacy in experimental conditions, clinical efficacy against epilepsy and non-epileptic diseases of major, classical and newer antiepileptic drugs (AEDs – lamotrigine, topiramate, levetiracetam, valproate and carbamazepine).

Methods. A literature search for publications written in English, preferably published within a period of the last fifteen years, using the key words listed below.

Review. The majority of AEDs possess more than one mechanism of action. They exert their effect by acting on various receptors (different types of glutamatergic and mainly $GABA_A$ receptors), neurotransmitters (mainly glutamate or GABA) and voltage-gated ion channels (sodium or calcium ion channels). All reviewed AEDs possess neuroprotective activity, the weakest being carbamazepine. Apart from epilepsy, AEDs may be also used in the pharmacotherapy of migraine, neuropathic pain, spasticity, psychiatric disorders and Parkinsons's or Alzheimer's diseases.

Conclusions. As highlighted above, around 30% of epileptic patients do not substantially benefit from AEDs. It is possible that rational combinations of AEDs, based upon experimental studies, could improve this outcome. The neuroprotective effects of AEDs may point to their disease-modifying activity.

Key words: antiepileptic drugs • clinical efficacy • animal seizure models • neuroprotection • mechanisms of action • non-epileptic conditions

INTRODUCTION

Epilepsy is a chronic and often progressive neurological disorder characterised by recurrent spontaneous seizures, resulting from excessive, uncontrolled electrical activity in the brain (Löscher and Potschka, 2002; Löscher, 2002; Murakami et al., 2007). It is generally defined by the occurrence of at least one unprovoked seizure (Fisher et al., 2005). Seizures can originate in one or more region of one or both hemispheres, or begin simultaneously in both hemispheres (Löscher and Potschka, 2002). However, the most epileptogenic area of the brain is the medial temporal lobe (Löscher and Potschka, 2002; Cascino, 2008; Curia et al., 2008). Sub-

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sequently convulsions are generally classified into partial (simple, complex and secondarily generalized), the most common, generalized (tonic, clonic, tonic-clonic, absence, myoclonic and atonic) and unclassified seizures (Kwan and Brodie, 2000; Wojtal et al., 2006). Epilepsy not only affects brain physiology but it also influences human social, vocational and psychological functioning (Dudra-Jastrzębska et al., 2007). The main goal in the treatment of epilepsy is to attain seizure-freedom without producing antiepileptic drugs (AEDs) toxicity and without interfering with normal brain function (Małek et al., 2003; Cascino, 2008). The main two groups of AEDs are voltage-dependent sodium or calcium channel blockers e.g.: **carbamazepine (CBZ), gabapentin (GBP), lamotrigine (LTG), topiramate (TPM), valproate (VPA)** which block sustained repetitive firing in individual neurons and drugs enhancing inhibitory events mediated by GABA: TPM and VPA. Nevertheless, most of AED possess more than one mechanism of action (Czapinski et al., 2005). The treatment of choice in epilepsy is based upon chronic administration of AEDs (Löscher and Potschka, 2002).

In about 30% of patients, this effect fails to be achieved because of pharmacoresistance (Kwan and Brodie, 2000; Sabers and Gram, 2000; Rigo et al., 2002). There are many possible causes of refractory epilepsy, the most important ones seem to be genetic, disease-related and drug-related factors, which lead to insufficient seizure control (Löscher and Potschka, 2002). Mechanisms underlying the development of resistance are still elusive (Sabers and Gram, 2000; Rigo et al., 2002). In this situation, polytherapy is attempted in order to improve effectiveness. The polytherapy is based on combinations of AEDs with different mechanisms of action (Deckers et al., 2000; Małek et al., 2003). The most effective therapeutic scheme seems to be a combination of a sodium channel blocker with a GABA-ergic enhancer (Deckers et al., 2000). An additional way to deal with pharmacoresistance is by resective or disconnective surgery, which can provide substantial relief from seizures, functional improvement and increased quality of patients' lives. However, postoperative complications may be associated with substantial rate of morbidity and even mortality, thus the risk/benefit ratio should always be taken into consideration (Lee et al., 2008b). Vagus nerve stimulation on the other hand is a well-tolerated and effective therapeutic alternative for epilepsy patients refractory to both medical and surgical treatments, although its mechanisms

of action are still not fully understood. Moreover, vagus nerve stimulation possesses cumulative efficacy with time (Lee et al., 2008c; Mapstone, 2008). Irrespective of the treatment followed, patients are considered free of seizures if they had not had seizures of any type for a minimum of one year while receiving the same dose of AEDs or while not taking any medication (Kwan and Brodie, 2000).

AIM
Our goal was to provide data from the relevant studies, preferably within the latest fifteen years, on AEDs: LTG, TPM, LEV, VPA and CBZ, in respect to their mechanisms of action, human studies, activity profile in seizure models and their possible neuroprotecive activity.

METHODS
A literature search for publications written in English, preferably published within a period of the last fifteen years, using PubMed database and following key words: antiepileptic drugs, clinical efficacy, animal seizure models, neuroprotection, mechanisms of action, non-epileptic conditions.

REVIEW

Mechanisms of action of AEDs

LTG [3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine] is a novel, second generation AED. It is assumed that LTG's antiepileptic effect is mainly due to blocking the voltage sensitive sodium channels most effectively in depolarized cells, resulting in the presynaptic inhibition of excessive release of excitatory amino acids, particularly glutamate and aspartate (Czapiński et al., 2005; Lasoń et al., 2011). LTG also affects GABA-mediated synaptic transmission but there are conflicting reports as to whether inhibitory transmission is enhanced or suppressed by LTG, and this drug has also been found to block glutamate AMPA receptors and reduce glutamate release in the rat dentate gyrus (Lee et al., 2008a).

TPM [2,3:4,5-bis-0-(1-methyl-ethylidene-)-B-D-fruktopyranose sulfamate] is a newer AED, whose anticonvulsant effect depends on diverse mechanisms: negative modulatory effect on AMPA subtype of glutamate receptors (Schneiderman, 1998; Skradski and White, 2000; Świąder et al., 2005), attenuation of voltage – gated Na^+ currents (Leach and Brodie, 1995), inhibition of carbonic anhydrase (CA) isozymes, especially,

Table 1. Mechanisms of action of antiepileptic drugs

	Lamotrigine	Topiramate	Levetiracetam	Carbamazepine	Valproate
Na$^+$ channels	–	–		–	–
GABA receptors	+/–	+	+		– (only increase in GABA level)
Ca^{2+} channels	– N, P/Q, R, T-types	– (L-type)	– (N-type, partial)	–	– (T-type)
K$^+$ channels		+		+	+
Glutamate receptors	– (AMPA)	– (AMPA)			– (NMDA)
Other		– CA II and CA IV	Modulates SV2A binding site		– protein kinase C

(+) activator; (–) inhibitor; () no effect, CA – carbonic anhydrase. Data presented in Table 1 was based on Czapiński et al., (2005) and Lasoń et al. (2011)

CA II and CA IV (Bialer et al., 2004), inhibition of aspartate and glutamate release from the neuronal terminals (White et al., 1997), enhancement of GABA$_A$-mediated neurotransmission (Sabers and Gram, 2000; Li et al., 2002), inhibition of neuronal L-type high voltage-activated Ca^{2+} channels and modulatory effect on K$^+$ channel currents (Zhang et al., 2000).

LEV [(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide] is a novel AED with a unique mechanism of action. Recent studies have demonstrated that the most relevant LEV mechanism of action is through binding to the synaptic vesicle protein SV2A (Lynch et al., 2004). However, it remains unknown how LEV modulates SV2A (Bialer et al., 2004). This drug has other mechanisms of action that likely play a smaller role: reversing the inhibition of neuronal GABA – and glycine-gated currents by the negative allosteric modulators zinc and beta-carbolines (Rigo et al., 2002), and partial depression of the type-N calcium current (Niespodziany et al., 2001; Lukyanetz et al., 2002).

CBZ [5H-dibenzo[b,f]azepine-5-carboxamide] is a conventional, first generation AED, which is still widely used. The most important mechanism of action is stabilization of the hyper-exited neuronal membranes by blocking voltage sensitive Na$^+$ channels (Trojnar et al., 2002). This action inhibits both repetitive neuronal firing and the spread of discharges (Macdonald and Kelly, 1995). It also increases K$^+$ conductance, modulates Ca^{2+} channel function (Czapiński et al., 2005; Stępień et al., 2005; Dudra-Jastrzębska et al., 2007) and reduces glutamatergic transmission through NMDA-activated currents in cultured spinal cord neurons (Łuszczki et al., 2005). The pharmacologically active form of CBZ, oxidated by cytochrome P450 (Sardo and Ferraro, 2007) (by its isoforms CYP3A4 and CYP2C8), is carbamazepine-10,11-epoxide (CBZE).

CBZE is catalysed by microsomal epoxide hydrolase to inactive trans-carbamazepine-10,11-diol (CBZD). CBZ and CBZD are urine flow dependant, about 1 mL/min and 8 mL/min respectively, but CBZD is relatively independent of urine flow (Stępień et al., 2005; Perucca, 2006; Zaremba et al., 2006; Tutor-Crespo et al., 2008).

VPA (2-propylpentanoic acid) is one of the most commonly used older AEDs (Xia et al., 2006). As for the molecular mechanisms of action of VPA, the drug locks the voltage-dependent Na$^+$ and Ca^{2+} channels and activates K$^+$ conductance in neurons (Dudra-Jastrzębska et al., 2007), potentiates GABA-ergic transmission in specific brain regions, increases synthesis of GABA by activating the GABA-synthesizing enzyme glutamic acid decarboxylase and increases the potassium-induced release of GABA in cortical neurons (Wilby et al., 2005; Łuszczki et al., 2009), inhibits enzymes involved in GABA degradation including GABA-transaminase and succinic semialdehyde dehydrogenase (Owens and Nemeroff, 2003; Łuszczki et al., 2009). In addition, VPA reduces the level and release of the excitatory amino acid aspartate in the brain and attenuates neuronal excitation by the reduction of activation of NMDA receptors (Czapiński et al., 2005; Łuszczki et al., 2009). There is also a theory that VPA is connected with protein kinase C (PKC), mainly as its inhibitor (Löscher, 2002; Toth, 2005).

Human studies

LTG is widely used for seizure control in epilepsy, especially in patients with generalized tonic-clonic seizures and partial convulsions with or without secondary generalization, and in other neurologic and psychiatric disorders (Zakrzewska et al., 1997). This AED is used as add-on treatment for patients with refractory epilepsy and as monotherapy in newly diagnosed epi-

lepsy (Brodie and Schachter, 2001). It has been found to have similar effectiveness to valproic acid. Dinnerstein et al. (2007) described a case of LTG intoxication provoking status epilepticus in an adult with localization – related epilepsy. Their article demonstrated the proconvulsant effects of LTG therapy, mostly in childhood conditions such as benign focal epilepsy of childhood with centrotemporal spikes, severe myoclonic epilepsy of infancy, Lennox-Gastaut syndrome and juvenile myoclonic epilepsy. Moreover, nonconvulsive status epilepticus has been associated in 3 patients with idiopathic generalized epilepsy. The data also indicate that LTG can be effective in neuropathies. It was significantly better than placebo in the management of trigeminal neuralgia (Zaremba et al., 2006). In two other studies, significant reduction of pain has been also shown in patients with HIV-associated neuropathy (Sindrup and Jensen, 2002) and poststroke pain (Vitezic et al., 2008). The dose of LTG was usually 50 mg/day and increased by 50 mg weekly up to 300–400 mg. Calabrese et al. (1999) provided data from 199 patients that LTG was an effective treatment for bipolar depression and safe, because it did not increase the risk of inducing mania. Morover, data suggest that combined treatment of LTG and lithium can be beneficial for patients with bipolar disorder (Bialer et al., 2004). In patients with Alzheimer's disease, cocaine addiction and mood disorders, LTG was associated with promising outcomes (Margolin et al., 1998; Frye et al., 2000). Lampl et al. (2005) have indicated that LTG is highly effective in reducing migraine aura and migraine attacks.

TPM is efficacious in patiens with various types of epileptic attacks, especially in patients with refractory chronic partial epilepsies in short-term controlled clinical trials (Kelly et al., 2002; French et al., 2004; Majkowski, 2004a; Stępień et al., 2005). Bootsma et al. (2004) have reported that long-term retention, efficacy and side effect profiles for TPM have not been sufficiently investigated. They concluded that TPM was associated with a high incidence of side effects in clinical practice. The data have provided evidence, that TPM is effectively used as monotherapy in newly diagnosed adolescents and adults with partial or mixed seizures (Stępień et al., 2005). French et al. (2004) stated that TPM was appropriate for adjunctive treatment of refractory partial seizures in adults and effective for the treatment of refractory partial seizures in children. Another study evaluated the effectivevenss of TPM (200 mg/day) added to CBZ (without or with an additional AED) in 264 patients with localization-related epilepsy in a multicenter, double-blind, and placebo-controlled trial (Majkowski et al., 2005). The main finding of this study has revealed that most of the adverse effects ascribed to TPM have a tendency to disappear over time. TPM is also an effective option for patients with juvenile myoclonic epilepsy (Biton and Bourgeois, 2005; Sousa Pda et al., 2005). Noteworthy, TPM is effective practically against all types of epileptic seizures (Czapiński et al., 2005). In other interesting studies, TPM was administered to eight patients with trigeminal neuralgia – the doses ranged from 50 to 100 mg a day. The authors suggest that TPM can be considered an alternative treatment for patients with trigeminal neuralgia (Domingues et al., 2007). However, there were no beneficial effects of TPM in patients with trigeminal neuralgia in the multicenter, double-blind study (Gilron et al., 2001; Zaremba et al., 2006). TPM proved to be effective in the treatment of chronic daily headache (CDH) due to probable chronic migraine and with probable medication abuse in de novo migraine patients (Gracia-Naya et al., 2007). Similarly, the Dahlof et al. (2007) study has shown that TPM at a daily dose of 100 mg significantly improved daily activities in patients with migraine. Daily function and health status significantly improved for those achieving a > or = 50% migraine frequency reduction. Ferraro and Di Trapani (2008) have reported, that TPM is effective in the preventive treatment of pediatric migraine. TPM dosages (2–3 mg/kg/day) are much lower than the doses recommended for the adjunctive treatment of epilepsy (5–9 mg/kg/day).

LEV is recommended as an add-on therapy in refractory partial epilepsy (Otoul et al., 2005). It has been also demonstrated effective as adjunctive therapy for primary generalized tonic-clonic seizures and myoclonic seizures of juvenile myoclonic epilepsy. Other studies have indicated that intravenous LEV (at a dose of 1000–1500 mg administered over 5 minutes) may be considered in the treatment of nonconvulsive or focal status epilepticus refractory to initial therapy (Marson et al., 2001; Zaccara et al., 2006). Hawker et al. (2003) have demonstrated that LEV is effective in reducing phasic spasticity but not tonic spasticity in patients with multiple sclerosis.

CBZ is effective in the treatment of simple or complex partial seizures (Marson et al., 2007; Wheless et al., 2007) and secondarily generalized tonic-clonic seizures in adults and children (Sobaniec et al., 2005; Tutor-Cre-

spo et al., 2008). In the survey performed by Wheless et al. (2007), the experts choose CBZ as the drug of choice for initial monotherapy in partial seizures. Pain relief or a reduced pain ratio occurs at a CBZ dose of 100–2400 mg in 70% of patients, in contrast to those receiving placebo. Moreover, the doses between 100 and 400 mg per day showed effectiveness in relieving paresthesia (*Restless legs syndrome* – RLS) (Zaremba et al., 2006). In addition, CBZ can also be used in various disorders like acute mania, trigeminal neuralgia, nocturnal enuresis or prophylaxis of manic-depressive disorders unresponsive to lithium (Sobaniec et al., 2005). CBZ proved to be effective in bipolar disorder; a survey of 400 patients showed that approximately 70% responded positively (Zaremba et al., 2006). However, in patients with schizophrenia CBZ showed a decrease in aggressive behaviour, anxiety and depression, but did not affect the main symptoms (hallucinations and delusions) (Zaremba et al., 2006). There were many studies to determine other therapeutical effects of CBZ but they showed lack of effectiveness in Binge eating disorder (BED), post-herpetic neuralgia and only marginal analgesic effect in painful diabetic neuropathy (Zaremba et al., 2006). CBZ was the first AED used in bipolar disorder. There were many double-blind studies confirming the efficacy of CBZ and its derivate-oxcarbazepine. Moreover, a significant positive response was achieved in 70% of over 400 patients with mania. CBZ also showed similar therapeutic effects as lithium and chlorpromazine (Zaremba et al., 2006). The studies conducted in schizophrenic patients showed that administration of CBZ could reduce anxiety, aggressive behavior and depression. Again, there is no effect of this AED against other psychotic symptoms like hallucinations and delusions. Consequently, CBZ should be recommended in the form of combined therapy with neuroleptics, only in patients demonstrating hyperactivity, violent outbursts and affective symptoms (Zaremba et al., 2006).

VPA is recommended as the treatment of choice for generalized tonic-clonic seizures, absence seizures, and myoclonic seizures (Vazquez, 2004; Blaheta et al., 2005). The data show that VPA is effective and is associated with acceptable tolerability as first-line monotherapy in focal onset epilepsy, also (Jędrzejczak et al., 2008).

With regards to migraine prophylaxis, VPA has shown its effectiveness in two double-blind, placebo-controlled studies. The significant reduction of days with migraine headaches and good toleration were re-ported in both studies (Zaremba et al., 2006). As for bipolar disease, VPA is approved for the treatment of its manic phase (Lin et al., 2006). Two randomized, multicenter, double-blind clinical trials confirmed that overall outcomes were significantly better than in the placebo group (Bowden et al., 2000; Zaremba et al., 2006). There are some case reports showing effectiveness of VPA in the treatment of trigeminal neuralgia, post-herpetic neuropathy and other neuropathies. In some patients, VPA relieved pain, although other studies show that there is no significant effect in placebo-controlled trial (Zaremba et al., 2006). VPA is commonly administered as combination therapy for the treatment of schizophrenia, especially in aggressive patients. However, there is no significant evidence that VPA is efficacious based on large placebo-controlled trials (Zaremba et al., 2006). Slow-release VPA signifcantly decreased the subjectively rated intensity of RLS complaints and duration of symptoms compared to placebo (Eisensehr et al., 2004; Conti et al., 2008). The combination of VPA and amiloride compared to VPA alone, is associated with an increase in protective action against MES-induced seizures (Macdonald and Kelly, 1995).Additional data show that VPA inhibits the proliferation of cultured human neuroblastoma cells in vitro and in vivo (Cinatl et al., 2002; Eyal et al., 2006). Eyal et al. (2006) have reported that VPA increased P-glycoprotein expression and function in human tumour cell lines and in rat liver.

Activity profile of AEDs in seizures models

LTG is effective against maximal electroshock (MES)-induced seizures, which may be regarded as an experimental model of generalized tonic-clonic seizures and, to a certain degree, of partial seizures with or without secondary generalization (Löscher et al., 1991). It has been shown, in animal models, that LTG is less effective against generalized tonic clonic seizures when NMDA-mediated neurotransmission is augmented (Tomczyk et al., 2007). In the MES test, Borowicz et al. (2002b) evaluated the influence of aminophylline on the protective activity of LTG. The data indicate that aminophylline reduced the anticonvulsive effect of this drug in the MES test in mice. However, in contrast to aminophylline, another methylxanthine derivative, caffeine (1,3,7-trimethylxanthine) did not affect the protective action of LTG against MES in mice (Jankiewicz et al., 2007). Sardo and Ferraro (2007) suggested a relationship between the nitric oxide (NO) system and

the anticonvulsant effect of LTG which could be enhanced by reducing NO levels and, conversely, dampened by an increased nitrergic activity. They used an experimental model of partial complex epilepsy: the maximal dentate gyrus activation (MDA). Łuszczki et al. (2008) evaluated interactions of the NMDA receptor antagonist MRZ 2/576 (8-chloro-4-hydroxy-1-oxo-1,2-dihydropyridazinol (4,5 – b) quinoline-5-oxide choline salt) and LTG in the MES model. In this test, MRZ did not significantly affect the antiseizure effects of LTG. Among three calcium channel inhibitors studied, only amlodipine in subthreshold doses was able to potentiate the anticonvulsant activity of LTG in mice against MES, whilst diltiazem and amlodipine were ineffective (Łuszczki et al., 2007b). The aim of the Vitezic et al. (2008) study was to investigate the Na^+-K^+-ATPase activity in the hippocampus and cortex of rats following kainic acid (KA)-induced convulsions. Further, this study was also designed to investigate the influence of LTG pre-treatment on the mentioned hippocampal and cortex changes. KA systemic application resulted in Na^+, K^+-ATPase activity inhibition in the rat hippocampus and cortex and LTG pre-treatment was associated with a partially protective effect on enzyme activity.

In animal models of epilepsy, TPM is effective against major experimental convulsive procedures: MES-induced seizure, audiogenic seizures in DBA/2 mice, amygdala – kindled rats and pentylenetetrazole (PTZ) – induced convulsions (Nakamura et al., 1994; De Sarro et al., 2000). Experimental data have shown that TPM enhances the protective potential of conventional AEDs in animal models of epilepsy. Łuszczki et al.(2009) have demonstrated synergistic cooperation of TPM and gabapentin (GBP) in MES – induced seizures in mice. However, it is inactive or weakly active in seizures induced by picrotoxin (PTX), pentetrazole (PTZ), bicuculline (BIC) and strychnine (Sills et al., 2004; Stępień et al., 2005). No pharmacokinetic interactions among these AEDs and lack of acute adverse effects, make the combination of TPM and GBP very important for patients with refractory epilepsy (Sills et al., 2004).

Świąder et al. (2005) in their study have indicated that N-methyl-D-aspartate (NMDA) and KA, which are glutamate receptor agonists, and the $GABA_A$ receptor antagonist – bicuculline (BIC), reduced the antiseizure potency of TPM against MES in mice. Recent experimental data have shown that caffeine, a methylxanthine derivative, decreased the protective potential of TPM against MES in mice (Chrościńska et al., 2007; Jankiewicz et al., 2007).

Czapiński et al. (2005) have reported that **LEV** is effective against amygdala-kindling in rats and in genetic models of epilepsy. However, this AED is ineffective against MES- induced seizure or the clonic phase of seizures provoked by picrotoxin (PTX) or by other chemical convulsants. Other interesting studies have indicated that the anticonvulsant efficacy of LEV is synergistically and substantially enhanced by GABA-ergic drugs in amygdala-kindled rats and audiogenic seizures in mice. In a rat model of experimental status epilepticus, the combination of LEV and diazepam (DZP) is associated with anticonvulsant synergy (Patsalos, 2004). Doheny et al. (2002) have shown, that LEV administration was associated with a dose-dependent reduction in the frequency of generalized and non-generalized seizures in the tetanus toxin seizure model, which is considered to reflect human complex partial epilepsy. Other data have indicated that LEV did not impair cognitive functions in experimental animals or epileptic patients (Czapiński et al., 2005).

The duration of EMG (electromyographic activity) induced by MES was shortened by **CBZ** at a dose of 20 mg/kg. Similar effects were observed in the duration of tonic extension seizures. Strange as it may seem but almost the same effects were observed by administrating CBZ orally (Murakami et al., 2007). In the MES test in mice D-(–)-3-(2-carboxypiperazin-4-yl)propyl-1-phosphonate (D-(–)CPP) and D,L-3-(±)-(2-carboxypiperazin-4-yl)propyl-1-phosphonate ((±)-CPP), both competitive NMDA receptor antagonists, at a dose of 0.625 mg/kg potentiated the anticonvulsive action of CBZ, without influencing its plasma levels and producing significant adverse effects. Moreover, D-CPP even at the dose of 1 mg/kg was free of adverse effects but still enhanced the anticonvulsive actions of CBZ (Wojtal et al., 2006). Borowicz et al. (2007b) have demonstrated that both acute and chronic fluoxetine, a serotonin uptake inhibitor, enhances the anticonvulsive action of many AEDs, including CBZ. In an acute and chronic experimental protocol, fluoxetine (at 15 mg/kg) reduced the ED_{50} value of CBZ by 76,5% and 22.5% respectively. However fluoxetine increased the brain concentration of CBZ, pointing to a pharmacokinetic mechanism of this interaction. In another study, Borowicz et al. (2007a) showed that mianserin at 30 and 40 mg/kg elevated the electroconvulsive threshold; however, when administered at its subeffective dose of 20 mg/kg, the anticonvulsant action of CBZ was enhanced and a lowering of its ED_{50} value by 53% occurred. In contrast, chronic administration

of mianserin (30 mg/kg) did not lower the electroconvulsive threshold. After acute administration, the antidepressant at subeffective doses diminished the anticonvulsant activity of CBZ (Borowicz et al., 2007a). 2-Chloro-N6-cyclopentyladenosine (CCPA, a selective adenosine A1 receptor agonist) administered at a subthreshold dose of 0.125 mg/kg potentiated the anticonvulsant activity of CBZ against MES. Systemic administration of DPCPX (a selective A1 receptor antagonist) reversed the action of CCPA. CBZ in combination with CCPA did not interfere with the normal behavior of animals, since neither motor coordination nor long-term memory were altered (Łuszczki et al., 2005). The protective activity of CBZ against MES in mice is also significantly increased by 2-chloroadenosine (a non-selective adenosine A1/A2 receptor agonist) at a dose of 0.125 mg/kg. At the higher dose (1 mg/kg), 2-chloroadenosine is able to augment the anticonvulsant effect of CBZ against pentylenetetrazol-evoked seizures. The potentiated protective action of CBZ is reversed by aminophylline, a non-selective adenosine receptor antagonist (at 5 mg/kg), and 8-cyclopentyl-1,3-dimethylxanthine (8-CPX), a selective A1 adenosine receptor antagonist (at 5 mg/kg). 2-Chloroadenosine administered with or without AEDs did not cause either motor or long-term memory impairment (Borowicz et al., 2002a). Chronic amiloride, at the dose of 75 and 100 mg/kg, significantly enhanced the protective action of CBZ against MES-induced seizures, which was however accompanied by an increase in total CBZ brain concentration (Łuszczki et al., 2009). In the study performed by Łuszczki et al. (2008) agmatine showed no effect on the anticonvulsant action of CBZ in MES test in mice. On the other hand, some competitive NMDA receptor antagonists (such as LY235959, LY233053, D-CPP-ene, and procyclidine) enhanced the anticonvulsant action of CBZ in the MES test in mice.

VPA exerts anticonvulsant effects in almost all animal models of seizures such as MES, PTZ and amygdala-kindling (French et al., 2004).

Łuszczki et al. (2008) evaluated interactions of agmatine and VPA in the MES seizure model. In this experiment, agmatine enhanced the antiseizure activity of VPA. Moreover, some competitive NMDA receptor antagonists (such as LY235959, LY233053, D-CPP-ene and procyclidine) also augmented the anticonvulsant activity of VPA. The anticonvulsant effect of VPA is significantly increased by dizocilpine (MK-801), an open NMDA receptor channel blocker, in doses of 0.0125

and 0.05 mg/kg. Łuszczki et al. (2007b) have reported that furosemide, administered at a dose of 100 mg/kg markedly potentiated the anticonvulsant effects of VPA, however, other AEDs were unaffected. Noteworthy, furosemide did not affect the free plasma and total brain VPA concentrations (Łuszczki et al., 2007a). The combination of VPA and amiloride, as opposed to VPA alone, has shown an increase in its protective action against MES-induced seizures (Łuszczki et al., 2009). The anticonvulsant action of VPA is similar to that of CBZ in that it was potentiated by D-CPP and CPP (two uncompetitive NMDA receptor antagonists at 0.625 mg/kg) in the MES test in mice, without any pharmacokinetic mechanisms involved. Moreover, D-CPP, even at the dose of 1 mg/kg, was free of adverse effects but still enhanced the anticonvulsant activity of VPA. However, in contrast to CBZ, VPA, in combination with CPP or D-CPP caused a moderate motor impairment (with CPP) and a significant impairment of long-term memory and motor coordination (with D-CPP) (Cinatl et al., 2002). Administration of fluoxetine, both acutely and chronically, enhances the anticonvulsive action of VPA. In the acute and chronic experimental protocol, fluoxetine, both at 15 mg/kg, reduced the ED_{50} value of VPA by 28.1% and 20%, respectively (Borowicz et al., 2007b). Borowicz et al. (2007a) showed that mianserin, at 30 and 40 mg/kg, elevated the electroconvulsive threshold, however, when administered at its subeffective dose of 20 mg/kg, it enhanced the anticonvulsant action of VPA and lowered its ED_{50} value by 24% against MES. In contrast, chronic application of mianserin at 30 mg/kg, resulted in a reduction of the anticonvulsant action of VPA by 33% (against MES in mice). Tricyclic antidepressants, given acutely, imipramine and amitriptyline but not desipramine, potentiated the protective efficacy of VPA against MES-induced seizures. There are data showing negative influence of VPA on total distance moved by mice and the velocity, even after drug withdrawal. The significant TH immunoreactive cell loss in the substantia nigra suggests cell death in the motor system is occurring (Eyal et al., 2006).

Mechanisms of action of AEDs on neuroprotection
In the Papazisis et al. (2008) study a well-established model of perinatal asphyxia in 7-day-old rats was used to investigate the effect of **LTG** on hypoxic-ischemic (HI)-induced damage to different hippocampal brain structures. Their results suggest a neuroprotective ef-

fect of LTG in this particular animal model of neonatal HI encephalopathy. Another interesting study has demonstrated that sipatrigine (BW619C89), a derivative of LTG, has potent neuroprotective properties in animal models of cerebral ischemia and head injury (Calabresi et al., 2000). Lee et al. (2000) have indicated that LTG and MK-801 (dizocilpine) are effective in attenuation of brain lesions induced by 3-nitropropionic acid. A higher dose of LTG (20 mg/kg) is associated with a better neuroprotective effect than MK-801 (2 mg/kg per day). Other data reveal that LTG reduces hippocampal neuronal damage in animal models of cardiac arrest-induced global cerebral ischemia (Shuaib et al., 1995; Wiard et al., 1995; Crumrine et al., 1997; Trojnar et al., 2002). In a KA-induced model of status epilepticus in rats, LTG has reduced hippocampal neuronal loss even at doses not protecting from seizures. The authors suggest that seizure prevention and neuroprotection might not be tightly coupled (Maj et al., 1998). Another study has demonstrated that mild hypothermia associated with LTG treatment is more effective in neuroprotection than hypothermia or LTG alone. The authors conclude that the combination of LTG with mild hypothermia could increase its neuroprotective properties (Koinig et al., 2001).

Hanaya et al. (1998) have demonstrated that TPM dose-dependently reduces the severity of kindled seizures. The administration of TPM after experimental status epilepticus in adult male Wistar rats attenuates seizure-induced hippocampal neuronal injury (CA1 and CA3 area). Other studies have demonstrated that TPM, when administered post-insult in vivo, is protective against selective hypoxic-ischemic white matter injury (Follet et al., 2004; Stępień et al., 2005). Also, Leker et al. (2003) have underlined that TPM is effective in global and focal ischemia. Another interesting study has demonstrated that early administration of a neuroprotective agent in combination with later-onset cooling could represent an effective therapeutic intervention after neonatal hypoxia-ischemia (Liu et al., 2004). In a rat model of focal cerebral ischemia, TPM has also proved to be neuroprotective. Treatment with this drug, 2 hours after the right middle cerebral artery embolization, resulted in a dose and use-dependent protection of neurons (Yang et al., 1998).

Animal studies have shown that **LEV** is an effective neuroprotectant in focal ischemia (Leker and Neufeld, 2003). Other studies have shown that LEV exhibits neuroprotection in a rat model of focal cerebral ischemia

(Hanon and Klitgaard, 2001). Mazarati et al. (2004) have demonstrated that LEV possesses neuroprotective activity in experimental status epilepticus. However, Pitkanen (2002) has indicated that LEV did not reduce hippocampal damage after pilocarpine – induced status epilepticus when assesssed 3 weeks later.

CBZ protects only partially against pyramidal cell damage and seems to be less efficacious in terms of neuroprotection than the novel AED in experimentally-induced status epilepticus. Moreover, the drug protected neither against the hilar somatostatin-immunoreactive neuron loss nor the spatial learning deficit (Murakami et al., 2007). It has been documented that CBZ has neuroprotective properties in a model of ischemic stroke. Moreover, CBZ reduces cerebral perfusion and is a CNS depressant (Zaremba et al., 2006).

VPA, when given chronically, was shown to distinctly protect hippocampal neurons in rats subjected to self-sustaining status epilepticus, evoked by prolonged electrical stimulation of the basal amygdala (Morland et al., 2004). Interestingly, this clear-cut neuroprotection was associated with much better behavioral outcome (less hyperexcitability or locomotor hyperactivity) when compared to non-treated controls. Noteworthy, VPA did not suppress the following spontaneous seizure activity (Brandt et al., 2006). According to Bolanos et al. (1998), chronic administration of VPA did, however, inhibit the development of spontaneous convulsions in rats exposed to kainic acid-induced status epilepticus. Moreover, VPA decreased damage following transient focal cerebral ischemia or ischemia-reperfusion injury in the rat brain (Ren et al., 2004; Suda et al., 2013).

CONCLUSIONS

Epilepsy is one of the most common neurological disorders – it affects about 1% of the worldwide population, which is about 50 million people. Each year 20 to 70 per 100 000 incidents of the disease are registered. The therapy leading to long-standing remissions is achieved only in 70–80% of cases. The difficulties in the therapy of epilepsy arise from its yet mostly unknown etiology. Epilepsy is comprised of periodic disturbance in neuronal activity, which results from excessive discharges of brain cortex, limbic system or brain trunk neurons. For both first and second line treatment, conventional AEDs are used in generalized tonic-clonic seizures, simple partial complex partial seizures and myoclonic epileptic attacks (Kelly et al., 2002). Among these ther-

apeutic agents CBZ and VPA are prominent (Kelly et al., 2002). These AEDs act via diverse mechanisms of action, although the majority block voltage-dependent sodium channels and enhances GABA-ergic inhibitory neurotransmission. LTG, TPM and LEV are newer AEDs, whose anticonvulsant effect depends on a variety of mechanisms. Although a substantial amount of experimental data on the effective synergistic combinations of AEDs is available (Czuczwar et al., 2009a,b), there is an urgent need for multicenter studies and development of standards on this issue in drug-resistant epileptic patients (Majkowski, 2006). Drug resistance in epilepsy, although not entirely understood, seems to result from disturbed pharmacological targets (i.e. GABA receptors) or an overexpression of protein AED transporters (Majkowski, 2004b). Probably, synergistic AED combinations, derived from preclinical studies, could be of value to drug resistant epileptic patients, but this needs, as mentioned above, careful clinical verification.

An increasing role of AEDs in the treatment of other (besides epilepsy) conditions is emerging. Especially neurological and psychiatric disorders can benefit from these drugs. In neuropathies, VPA and LTG can be effective; these AEDs were also effective in the treatment of bipolar depression. The other AED – TPM has been used in patients with trigeminal neuralgia. In patients with Alzheimer's disease, cocaine addiction and mood disorders, LTG was associated with promising outcomes. Some AEDs are effective in reducing migraine attacks. These include: LTG, TPM and VPA. One of the second generation AEDs: LEV is effective for reducing phasic spasticity in patients with multiple sclerosis. CBZ is effective in acute mania, trigeminal neuralgia, nocturnal eneuresis and bipolar disorders. Perspectives for the use of novel AEDs in conditions other than epilepsy look promising. These drugs are recommended especially in disorders where the available treatment has proved to be ineffective.

One of the above presented AEDs, LTG, has a distinct neuroprotective profile in animal models of cerebral ischemia. This drug was also associated with neuroprotective effects in a KA-induced model of status epilepticus. Another AED, TPM, very potently prevented neuronal loss in hippocampus exposed to prolonged seizure activity (Remy and Beck, 2006). Additional data have demonstrated that TPM is protective against selective hypoxic – ischemic white matter injury (Domingues et al., 2007) and ischemia. Another new AED, LEV, is effective in focal cerebral ischemia.

Last, but not least, VPA displayed potent neuroprotective activity in models of status epilepticus and ischemia, also significantly affecting post-status epilepticus behavior. Neuroprotective effects of AEDs in seizure models, and especially that of VPA, may point to the epilepsy-modifying activity. However, the problem with neuroprotection by AEDs may be that a full extrapolation from animal studies to human conditions is not fully possible.

DISCLOSURES

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